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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,044	01/14/2002	Mirella Ezban	5994.504-US	1706

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NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,044	EZBAN ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Amendment filed September 23, 2004 has been entered. Claims 1-16 and 18-21 are cancelled. Claims 24-30 are new. Claims 17 and 22-30 are pending and have been considered in this Office Action.

Rejections Withdrawn

The rejection of Claims 17 and 18 under 35 U.S.C. 102(a) as being anticipated by Taniguchi et al. (Cancer Res. (1998) 58: 4461-4467) is withdrawn in light of the amendments. Taniguchi et al. do not teach detecting the increase in expression of a gene in the CCN gene family.

The rejection of Claims 17 and 22-23 under 35 U.S.C. 102(b) as being anticipated by Pendurthi et al. (Proc. Natl. Acad. Sci. (1997) 94: 12598-12603) is withdrawn in light of the amendments. The method of Pendurthi et al. would inherently result in an increase in Cyr61, however, Pendurthi et al. do not teach detecting the increase in expression of the Cyr61 gene as required by the present claims.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, and 22-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing expression of at least one gene in a cell line that constitutively expresses tissue factor, wherein the gene is selected from the group consisting of Cyr61, CTFG, dopamine D2 receptor, EST Incyte PD 395116 and P2U nucleotide receptor, does not reasonably provide enablement for a method of increasing expression of a gene in the CCN gene family in any cell under conditions that result in an increase in said expression.

Applicants contend that the rejection has been rendered moot by the current claim amendments. However, the claim amendments and new claims do not address the following issues raised in the previous enablement rejection:

The claims still are open to increasing gene expression in any cell (even those that do not express tissue factor) including in vivo methods. The specification does not provide enablement for regulating a gene in a cell other than a *cell line that constitutively expresses tissue factor (in vitro; see all claims)* or regulating the expression of any gene in any cell using FVIIa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The enablement rejection is repeated below with additional discussion addressing the lack of enablement of the new claims.

Breadth of the Claims:

Claim 17 encompasses a method of regulating the expression of a gene from the CCN gene family in any cell in vitro or in vivo using FVIIa. New Claim 30 is similar

except that the genes with increased expression are dopamine D2 receptor, EST Incyte PD 395116, and P2U nucleotide receptor. Claims 22-23 are narrowed from claim 17 to define the gene to be regulated but are still open to using any cell. New Claims 24-29 limit the method to in vivo gene regulation by administering FVIIa.

Nature of the Invention:

The nature of the invention involves the identification of several genes, including Cyr61, CTFG, dopamine D2 receptor, EST Incyte PD 395116, and P2U nucleotide receptor, that are upregulated in tissue factor expressing cell lines that are contacted with factor VIIa, The nature of the invention *requires* the interaction of tissue factor with its agonist (factor VIIa) for the upregulation of the genes described. The nature of the invention also involves the relationship of this upregulation to disorders such as burns and inflammation and to regeneration of vessel walls, and to pathological conditions related to chemotaxis.

Amount of Direction/Guidance Provided and Presence/Absence of Working Examples:

The present Specification provides guidance and working examples describing the upregulation of genes encoding Cyr61, CTFG, dopamine D2 receptor, EST Incyte PD 395116, the P2U nucleotide receptor, and the urokinase receptor gene in vitro. There is *no guidance or working examples* of regulating gene expression *in vivo or using cells lines that do not constitutively express tissue factor (Camerer et al. discuss the dependence of increased gene expression by Factor VIIa on the presence of tissue factor in the cell; See Discussion in Camerer et al. J. Biol. Chem. (1999) 274(45): 32225-32233; cited in Office Action mailed 3/25/04). The Specification only provides a*

general guidance as to the use of factor VIIa in treating burns or inflammation or in enhancing the regeneration of vessel walls or in pathological conditions related to chemotaxis and the Specification does not provide any working examples of successfully treating burns, inflammation or enhancing or inducing regeneration of vessel walls in patients or in treating patients with pathological conditions related to chemotaxis.

State of the Prior Art/Relative Skill of those in the Art:

As evidenced by Taniguchi et al. and Pendurthi et al. described in the prior art rejections above, those of skill in the art were aware at the time of the present invention that factor VIIa could be used to upregulate gene expression in vitro. Taniguchi et al. teaches that contacting factor VIIa with human pancreatic cell lines that overexpress tissue factor results in increased expression of the gene encoding the urokinase receptor. Pendurthi et al. teach that contacting a fibroblast cell line with factor VIIa results in the upregulation of the gene encoding poly(A) polymerase. However, upregulation of genes by factor VIIa appears to require tissue factor and proteolytically active factor VII (FVIIa) (see Camerer et al. (J. Biol. Chem. (1999) 274(45): 32225-32233 at p. 32231, Col. 2, paragraph 2). Camerer et al. show that while contact of FVIIa to cells expressing tissue factor upregulates egr-1 expression, active site inhibited FVIIa did not induce a response in egr-1 mRNA (see p. 32229, Col. 1, 3rd full paragraph). Pendurthi et al. (J. Biol. Chem. (2000) 275(19): 14632-14641) shows that factor VIIa catalytic activity is required for the induced expression of Cyr61 and that a factor VII modified with D-Phe-L-Phe-L-Arg chloromethyl ketone (active-site inactivated

FVIIa) did not induce expression of Cyr61 (see Fig. 6 and p. 14633, Col. 1, "Proteins"). *A search of the prior art indicates that the studies of factor VIIa induction of expression have only been in vitro and Camerer et al. indicates that it remains to be seen what the physiological impact of the in vitro observations will be since many physiological pathways seem to be affected by factor VIIa (*see Camerer et al. (1999), p. 32232, last paragraph).

Predictability/Unpredictability:

Regulation of gene expression by contacting a protein to a cell involves many different proteins in a signal cascade and is thus very complex. The effect changes in the signaling cascade make in the treatment of disease is even more complex. The mechanism of how factor VIIa upregulates the genes is poorly understood. Thus, the predictability of what genes could be regulated, what cells other than cell lines that constituitively express tissue factor could be used, and what diseases or disorders could be affected by FVIIa induced expression is highly unpredictable.

Quantity of Experimentation:

For the reasons stated above, the quantity of experimentation to practice the claimed invention is considered undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the characterization of the mechanism by which factor VIIa, through its contact with tissue factor, upregulates gene expression and further, what diseases or disorders are affected by this upregulation. It is this

additional characterization (that is required to predict with a reasonable expectation of success what tissue factor agonists or antagonists besides factor VIIa could be used in the method, what genes could be regulated by the method, and what disorders would respond to upregulation of the gene expression) that constitutes undue experimentation. Thus, the full scope of the claims is not considered enabled by the present Specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites the limitation "the cell" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Objections are Withdrawn

The objection to claim 22 is withdrawn.

Conclusions

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
December 6, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER